

REMARKS

In order to further distinguish Applicants' claimed invention from the prior art and to advance this case towards allowance, claims 1 and 7 have been further amended to require the cation exchange resin be particulate. New claims 23 and 24 further define the resin as being in the form of a finely divided powder, the powder consisting of spheroidal particles. Basis for these amendments can be found on page 5 of the Specification. Claims 1, 2 and 4-24 are pending.

Applicants' claims are directed to ophthalmic pharmaceutical compositions and methods wherein the compositions comprise a beta blocker, an anionic mucomimetic polymer and a particulate cation exchange resin.

With regards to the Examiner's rejection of the claims based on 35 USC 103, Applicants respectfully reiterate that the Michaels and the Schoenwald et al. references disclose sustained release ophthalmic compositions using high molecular weight polymers. Rankin discloses ophthalmic compositions which include a polystyrene sulfonate polymer. None of these patents disclose the use of a resin, and Rankin does not suggest the polystyrene sulfonate polymer can be used in the anionic polymer compositions of Michaels or Schoenwald et al. Therefore, combination of these references must be based on impermissible hindsight reasoning. Moreover, even if properly combined, the references are insufficient to negate patentability when the invention is considered as a whole under 35 USC 103.

Mamajek et al. disclose a drug dispensing device which is administered orally and consists of a polymer plus an "expanding agent" which can include resins, such as Amberlite^R. There is no disclosure of compositions similar to Applicants' (gels, pourable liquids or anhydrous salts). Additionally, there is no suggestion for the use of the device in topical ophthalmic applications. Samejima et

al. disclose microcapsules which are, like Mamajek et al., administered orally. The microcapsules consist of ethylcellulose with a swellable polymer which is preferably in the form of a fine powder. Again, there is no suggestion the microcapsules can be used for topical ophthalmic applications.

In support of Applicants' assertions that the claimed combination results in improved compositions and methods for controlling and lowering intraocular pressure ("IOP") in that the compositions provide both sustained release and increased comfort, Applicants submit with this Supplemental Amendment the Declaration under 37 CFR 1.132 of Larry A. Bruce. In the Declaration, data supporting both the sustained release properties and the increased comfort of the claimed compositions are presented.

With regards to sustained release, the results of two studies are presented. The first is an *in vivo* animal study which compares the ocular bioavailability of a 0.25% betaxolol suspension encompassed by the claims of the present invention with a 0.5% betaxolol aqueous solution, known as BETOPTIC^R. The results of the study show that the 0.25% suspension provides for aqueous humor concentrations equivalent to the 0.5% aqueous solution due to the sustained release characteristics provided by the Amberlite^R and Carbopol present in the suspension. This conclusion is further supported by a clinical study in which the IOP of human glaucoma patients dosed with the 0.25% suspension and those with the 0.5% aqueous solution were compared. The average IOP values for both groups were significantly reduced and were not drastically different from each other at the respective measurement times, demonstrating that the 0.25% suspension is as effective in lowering IOP as the 0.5% solution.

With regard to Applicants' claim that the compositions provide for increased comfort, the Declaration presents data from ongoing human clinical studies which include the evaluation of the

subjective discomfort of patients administered the 0.25% suspension. These results are compared with subjective discomfort studies done with the 0.5% solution. In the studies with the 0.25% suspension, it was found that only 7.9% of the patients with primary open angle glaucoma reported discomfort when using the 0.25% suspension. In contrast, prior studies have shown 1 in 4 patients (25%) experienced discomfort on administration of the 0.5% solution. Therefore, it can be seen that the use of the 0.25% suspension, when compared with the 0.5% solution, provides for a decrease in subjective discomfort of about 68%.

Applicants submit that the data set forth and explained in the Declaration of Larry Bruce supports Applicants' assertion that the claimed compositions provide for both sustained release and increased comfort.

WHEREFORE, Applicants' claims are in condition for allowance and notice of such allowance is respectfully requested.

Respectfully submitted,
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